Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among children <18 years old, what is the efficacy/effectiveness and safety of COVID-19 vaccines compared to placebo in preventing COVID-19?

Review by: Mary Anne Castor, MD, Marie Carmela Lapitan, MD

RECOMMENDATIONS

We recommend the use of the BNT162b2 (Pfizer/BioNTech) vaccine, [given as 0.3 mL (30 ug) intramuscular injections, in 2 doses, 21 days apart] for children 12-15 years old to prevent symptomatic SARS-CoV-2 infection. *(Moderate certainty of evidence; Strong recommendation)*

We suggest the use of the mRNA-1273 (Moderna) vaccine, [given as 0.5 mL (100 ug) intramuscular injections, in 2 doses, 28 days apart] for children 12-17 years old to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

We suggest against the use of Coronavac (Sinovac), [given as 0.5 mL (600 SU) intramuscular injection, in 2 doses, 28 days apart] for children 3-17 years old to prevent symptomatic SARS-CoV-2 infection. *(No evidence; Weak recommendation)*

Consensus Issues

The issue of myocarditis associated with the mRNA vaccines in children was a major consideration in the recommendation, particularly with the mRNA-1273 (Moderna) vaccine. Despite the low incidence of post-vaccination myocarditis, some Panel members considered it significant enough, especially when normal children are concerned, to weigh heavily on the benefit risk ratio. The suspension of the use of mRNA-1273 among children in some countries due to the myocarditis issue was also raised, resulting in the cautious recommendation given for this vaccine. The Panel emphasized that warnings should be given to the parents and caregivers of the vaccine recipients to consult immediately in case of symptoms occurring after vaccination, which may suggest the development of myocarditis.

Key Findings

This review provides the evidence on the use of COVID-19 vaccines in children based on one (1) systematic review, three (3) randomized controlled trials (RCTs), two (2) real world effectiveness studies, five (5) case series/reports, and six (6) regulatory agency reports. Findings show that BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) provide sufficient protection against COVID-19 infection among adolescents who are at least 12 years old. More reactogenicity events were noted but adverse events were generally non-severe. Higher immunogenicity responses were also seen with children compared to adults. CoronaVac (Sinovac) was found to be immunogenic among children aged 3-17 years old.

Real world evidence on the use of mRNA vaccines in children supported the findings in the clinical trials. Myocarditis was detected among children after mRNA vaccination, although rare.

Introduction

COVID-19 affects more children than adults.[1] In the USA, children comprised 16.2% of the total cumulative cases of COVID-19.[2] In the recent months, adolescents already represent

a growing proportion of new COVID-19 cases.[3] Some of these cases can become severe or develop into the Multisystem Inflammatory Syndrome in Children (MIS-C).[1]

Aside from directly getting infected, children have also been affected because of the continued closure of face-to-face classes. Once children start going back to school, the risk of transmission among themselves as well as the possibility of bringing home the virus and causing household transmission is a concern to most parents, especially when there are households who are at risk of developing severe COVID-19, such as the elderly. Vaccinating these children may be one way of protecting these children as well as their household members. There is thus a need for a safe and effective vaccine for children.

Review Methods

The search of the literature performed on September 17, 2021 identified 18 reports on the use of COVID-19 vaccines in children and adolescents. One systematic review included two RCTs, two case series and four case reports.[4] All studies cited in this systematic review are included here, save for two case reports, which involved adults as well. Three randomized controlled trials were identified, one using BNT162b2 (Pfizer) [5], one mRNA-1273 (Moderna) [6], and one CoronaVac (Sinovac).[7] Five reports presented real-world evidence on the effectiveness and safety of BNT162b2(Pfizer) in children.[8-12] Seven reports on post-COVID-19 vaccination myocarditis were identified.[13-19] Search of the regulatory sites identified assessment reports providing vaccine efficacy and safety information on the pediatric use of BNT162b2 (Pfizer) [20] and mRNA1273 (Moderna).[21]

Six regulatory sites (WHO, US-CDC, NACI-Canada, UK-JCVI, EMA, and Singapore MOH) provided specific recommendations on COVID-19 vaccination in children.[21-26] One local recommendation from the Philippine Pediatric Society (PPS)-Philippine Infectious Disease Society of the Philippines (PIDSP) is also included.[27]

Search of the *clinicaltrials.gov* identified 21 active intervention trials on COVID-19 vaccination in the pediatric population.

Results

BNT162b2 (Pfizer)

Clinical Efficacy

One randomized placebo-controlled trial investigated the efficacy and safety of BNT162b2 (Pfizer) in the prevention of COVID-19 infection.[5,20] The trial randomized 2,264 children (vaccine group = 1,134; control group = 1,129). The overall quality of evidence of the RCT for BNT162b2 was downgraded to moderate because this was an interim report; for safety the quality of evidence was further downgraded to low because of imprecision.

The study reported a vaccine efficacy of 100% (95% CI 78.0-100.0) at least 7 days after the second dose, after a median follow up of 2 months, as no cases of COVID-19 infection occurred in the vaccine group. It also suggests potential sufficient protection after the single dose (VE = 75.1%, 95% CI 7.6-95.5). Efficacy against severe COVID-19 infection or COVID-19-related deaths could not be assessed since there were no cases reported during the study period.

Immunogenicity

The above study also demonstrated that BNT162b2 is highly immunogenic in children aged 12 to 15 years old, generating a GMT of 1283.0 at 1 month after dose 2, compared to a GMT of 15.1 in the placebo group and 730.8 in the 16 to 25 years old treatment group. It also compared immune responses to that of adults aged 16 to 26 years old and results showed that their responses were non-inferior with a neutralizing antibody geometric mean titer ratio (GMR) of 1.76 (95% CI 1.47–2.10). Non-inferiority criteria was set at a lower boundary of the two-sided confidence interval for the GMR of greater than 0.67.

Real World Evidence - Effectiveness

A retrospective case series of 31 long-term pediatric care facility residents with patients aged 16 to 25 years old showed that none among the vaccinated patients (all of which received BNT162b2) developed COVID-19, resulting in a vaccine effectiveness of 100%. Majority (83.9% and 74.2% after dose 1 and dose 2, respectively) did not have any adverse reactions to the vaccine after the first and second doses.[8]

A case series of 13 patients with solid tumors, 9 of which were aged 16 to 17 years old looked at the immunogenicity of BNT162b2 among patients with solid tumor under treatment or had completed their treatment within 6 months. Seroconversion rate after dose 1 was 60% and 90% after dose 2.[9]

One study looked at the US Coronavirus Disease 2019–Associated Hospitalization Surveillance Network (COVID-NET) data and reported that hospitalization rate among the unvaccinated adolescents were 10.1 times higher than those who were vaccinated in the US, where the only vaccine with an emergency use authorization (EUA) for adolescents aged 12 to 15 years old is BNT162b2.[10] A US-CDC study that looked at hospitalization and emergency department visits using the National Syndromic Surveillance Program and CDC data reported that emergency department visits and hospitalization rates were higher (3.4 and 3.7 times higher, respectively) in the states with lowest vaccination coverage compared to the states with the highest vaccination coverage.[11]

Safety, Clinical trial

In the randomized clinical trial on BNT162b2 among children aged 12 to 15 years old, patients who received BNT162b2 reported more local and systemic events than those who received placebo.[5,20] Most resolved within 1 to 2 days. The most common local adverse event reported by the vaccine group was pain at injection site (post D1 = 86%, D2 = 79%). The most common systemic adverse events were headache (post D1 = 55%, post D2 = 65%) and fatigue (post D1 = 60%, post D2 = 66%). Systemic events were reported more often after the second dose of BNT162b2 than the first dose. There were no deaths, hypersensitivity, myocarditis, thrombosis, or multisystem inflammatory syndrome in children (MIS-C) reported. One discontinuation from the study due to adverse event was in a patient with fever of greater than 40°C and was assessed as a vaccine-related event.

The US–FDA regulatory review reported the following rates of adverse events after administration of BNT162b2 in children: pain at injection site (90.5%), fatigue (77%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), lymphadenopathy (0.8%), and nausea (0.4%). Apart from the significantly higher reactogenicity rates compared with placebo, the BNT162b2 group also presented with higher numbers of patients developing lymphadenopathy.[20]

Safety, Real World Evidence

One retrospective case series described the adverse events reported by 31 patients aged 16 to 25 years old (mean age 21) admitted to a long-term pediatric care facility after vaccination with BNT162b2.[8] Majority did not report any side effects (83.9% post D1, 74.2% post D2). The most commonly reported adverse events were agitation and discomfort (9.7% post D1, 12.9% post D2)**,** nausea (6.5% post D1, 3.2% post D2), and fever (0% post D1, 6.5% post D2). The study also reported that none of the patients tested positive for COVID-19 nor developed any COVID-19 symptoms post-vaccination. The study, however, did not mention the duration of the follow-up after vaccination.

In the case series of 13 patients with solid tumors who received BNT162b2 vaccine, 5 did not report any adverse event. The most common reported adverse event was mild to moderate pain at the injection site, relieved after 1 to 2 days.[9]

A review of the reports to the Vaccine Adverse Event Reporting System (VAERS) and adverse events and health impact assessments reported in v-safe, which is a smartphone-based safety surveillance system showed that as of July 16, 2021, VAERS had received 9,246 reports for the Pfizer/BioNTech vaccine out of approximately 8.9 million adolescents vaccinated. Most were non-serious (90.7%) while 9.3% were serious adverse events including 4.3% for myocarditis. There were 63.4% local and 48.9% systemic reactions. For serious adverse events, the following were the common conditions or findings: chest pain (56.4%), increased troponin levels (41.7%), myocarditis (40.3%), increased C-reactive protein (30.6%), and negative SARS-CoV-2 test results (29.4%). There were 14 reports of death, all reviewed by CDC physicians. Causes of death were pulmonary embolism (2), suicide (2), intracranial hemorrhage (2), heart failure (1), hemophagocytic lymphohistiocytosis, and disseminated *Mycobacterium chelonae* infection (1), and unknown or pending further records (6). From the v-safe data, among 62,709 enrolled 12 to 15 year old children, there were 63.9% local reactions and 48.9% systemic reactions after the 1st dose. For the 2nd dose, systemic reactions were more common (63.4%). For ages 16 to 17 years old, systemic reactions were 55.7% after the 1st dose and 69.9% after the 2nd dose. The most frequently reported reactions for both age groups after either dose were injection site pain, fatigue, headache, and myalgia. Less than 1% required medical care with 56 (0.04%) needing hospitalization.[12]

mRNA-1273 (Moderna)

One Phase 2/3 randomized placebo-controlled trial was performed to assess the efficacy, immunogenicity, and safety of mRNA-1273 (Moderna) in the prevention of COVID-19 infection among adolescents aged 12 to <18 years old. The interim report has been published with additional information available from the EMA regulatory review report.[6,21] The characteristics of the study are presented in Appendix 2. The methodological assessment is presented in Appendix 3.

Clinical Efficacy

The study provided several measures of clinical efficacy for mRNA1273 (Moderna) against COVID-19 for adolescents aged 12 to 17 years. Point estimates of vaccine efficacy for symptomatic COVID-19 disease (VE = 92.7%, 95% CI 67.8-99.2), SARS-CoV-2 infection (VE = 69.8%, 95% CI 49.9-82.1), and asymptomatic SARS-CoV-2 infection(VE = 59.5%, 95% CI 28.4-77.3), showed sufficient protection. No severe cases nor deaths occurred in the study.

Immunogenicity

Non-inferiority for neutralizing and binding antibody level and seroresponse using the pseudovirus neutralization assay (both at ID50 and ID80), the spike IgG antibody ELISA, and the MSD Multiplex assay was demonstrated. A slightly lower seroresponse rate in the 12 to <16 year old subgroup was observed.

Safety, Clinical Trial

The incidence of local adverse reactions (ARs) was higher in the mRNA-1273 group compared with the placebo group after any and after each dose. The most frequently reported local solicited AR in the mRNA-1273 was injection site pain reported by 97.2% (93.1% post D1, 92.4% post D2). Majority of solicited local ARs were mild to moderate. The incidence of systemic ARs was higher in the mRNA-1273 group compared with the placebo group after any and after each dose. The most frequently reported systemic solicited adverse reaction in the mRNA-1273 group after any dose was headache. The incidence of solicited systemic adverse reactions was notably higher after dose 2 compared with dose 1. The majority of systemic solicited ARs was mild to moderate. Severity of systemic adverse events increased from dose 1 to dose 2. Grade 4 solicited systemic ARs were recorded for three (3) subjects in the mRNA-1273 group (fever, headache, and nausea/vomiting).

At the time of the report, no anaphylactic reaction, serious adverse events (SAEs) with fatal outcomes or deaths were reported. No cases of myocarditis have been reported, although three (3) participants who received the vaccine reported symptoms that could be consistent with myocarditis or pericarditis.

Coronavac (Sinovac)

A Phase 1/2 randomized controlled trial for CoronaVac in children aged 3 to 17 years old compared the reactogenicity and adverse reactions for the 1.5ug dose and the 3ug dose. The 3ug dose, which is the preparation currently available, resulted in higher neutralizing antibody titers and seropositivity rate compared to the 1.5ug and placebo groups. No clinical outcomes of efficacy was reported. Adverse reactions were similar in both the vaccine and placebo (alum) groups and were generally mild to moderate.[7]

ChAdOx1 (Astra Zeneca), Ad26-CoV2-S (Janssen/ Johnson&Johnson), Gam-COVID-Vac (Sputnik V)

The search failed to identify any study reporting on outcomes of the use of these vaccines in children or adolescents.

Adverse Events of Interest in Children : Myocarditis

Myocarditis was found to be an adverse event of special interest for mRNA vaccines, particularly in children.

One article reviewed four reports of myocarditis, including two on adolescents, which are included in this review.[16] Four case series of myocarditis included in this review which support the database review findings. The clinical presentation of the mRNA vaccine-associated myocarditis/pericarditis in children and adolescents is consistent across the available reports [17-19,28]. Majority of which were in males (>90%). Nearly all presented after the second dose, commonly within 7 days of the vaccination. The common symptoms included chest pain, fever, palpitation, shortness of breath, fatigue, nausea, and vomiting, often transient and self limiting. Median interval of the symptoms was 2 days.[14] All reported cases had elevated troponin and C-reactive protein levels. The most common abnormal ECG changes included ST-segment elevation and diffuse ST changes. On echocardiography, left ventricular function was normal. The clinical course was mild and all patients recovered and were discharged home in less than a week.

A study looked specifically at the VAERS reports for myocarditis among persons less than 30 years old vaccinated with either BNT162b2 or mRNA-1273. There were 62.8 cases per million second doses among males 12 to 17 years old. More than 90% of cases were males, majority (76%) occurring after the second dose and within 7 days of vaccination. Most would present with chest pain, fever, palpitations, and shortness of breath and these were generally mild. No deaths were reported.[14] Two more studies looked at database reports of myocarditis in different countries where mRNA vaccines are given to adolescents. Incidence of myocarditis in most of these countries showed that myocarditis is rare with less than 10 cases per million vaccinees, except for Israel and Australia, which had slightly higher cases.[15,29]

The CDC estimated the rate of mRNA-vaccine-associated myocarditis at 40.6 cases per million second doses for males aged 12 to 29 years old and 4.2 for females. The highest rate was found with males aged 12 to 17 years old at 62.8 cases per million.[14] The ACIP concluded that the benefit of vaccination still outweigh the risks, including the risk of myocarditis after vaccination for all age groups, given the benefit of preventing 5,700 cases of COVID-19, 215 hospitalizations, 71 ICU admisssions and 2 deaths over the risk of 56 to 69 cases of myocarditis with vaccination among males. Greater benefit / harm ratio was seen in women with the prevention of 8,500 COVID-19 cases, 183 hospitalizations, 38 ICU admissions, 1 death prevented over the risk of 8 to 10 cases of myocarditis with vaccination.[14,23]

Recommendations from Other Organizations

The following are recommendations / guidelines from regulatory agencies on the use of COVID-19 vaccines in children:

Table 1. Summary of Recommendations from other Organizations on the use of COVID-19 vaccines in children

Regulatory Agency	Recommendation
World Health Organization (WHO) as of September 2, 2021 [22,30]	• Consider COVID-19 in children aged 12 to 15 years of age only when high vaccine coverage with 2 doses has been achieved in the high priority groups • Children 12 to 15 years of age with comorbidities may be vaccinated
Advisory Committee on Immunization Practices (ACIP) US CDC as of May 12, 2021 [3, 20,23]	• Children ≥12 years with high risk medical conditions in Phase 1c priority • Children ≥12 years without medical conditions in Phase 2 priority
National Advisory Committee on Immunization (NACI) Canada as of August 27, 2021 [24]	• A complete series with an mRNA COVID-19 vaccine should be offered to adolescents 12 to 17 years of age who do not have contraindications to the vaccine. *(Strong NACI Recommendation)*
Joint Committee on Vaccination and Immunization (JCVI)-UK Medicines and Health products Regulatory Agency (MHRA) as of September 16, 2021 [25]	• Children 12 to 15 years old can receive their first dose of COVID-19 vaccine • Second dose is pending further evidence on the safety • Children 12 to 17 years old who are at risk should receive their second dose at an interval of at least 8 weeks • Children ≥12 years old who live with immunosuppressed individuals should be offered two doses of vaccine, 8 weeks apart
European Medicines Agency (EMA) [21]	• Extended indication for mRNA-1273 to include use in children aged 12 to 17 years old as of July 23, 2021 • Extended indication for BNT162b2 to include use in children aged 12 to 15 years old as of May 28, 2021
Singapore Ministry of Health [26]	• Pfizer-BioNTech/Comirnaty COVID-19 vaccine is safe for use on adolescents aged 12 to 15 years old • While there is a small increased risk of myocarditis or pericarditis following the administration of the vaccines, the local incidence rate remains low at 0.48 per 100,000 doses administered • As a precaution, all vaccine recipients, especially adolescents and younger men, should avoid strenuous physical activity for one week following each dose of the vaccine
Philippine Pediatric (PPS)-Philippine Infectious Diseases Society of the Philippines (PIDSP) as of September 6, 2021 [27]	• Children ≥12 years old may be considered for vaccination with any duly approved COVID-19 vaccine • However, due to the limited vaccine supply, the older and more vulnerable age groups be prioritized. • Once the country will have adequate vaccine supply, the roll out can be initiated in high transmission areas and should prioritize the adolescents that are qualified in the A3

	(children with comorbidities) and A1 (children of healthcare frontliners) category

Ongoing Trials

As of October 7, 2021, 21 vaccine trials involving children and an additional 11 trials involving both children and adults were registered in *clinicaltrials.gov.*

Research Gaps

The evidence to inform practice on the use of COVID-19 vaccines in children is still lacking :

1. Clinical efficacy and safety of ChAdOx1, Ad26.CoV2.S, Gam-COVID-Vac, CoronaVac, BBV152, BBIBP in children
2. Long term efficacy, effectiveness and safety of all COVID-19 vaccines in children
3. Clinical efficacy and safety of COVID-19 vaccines in children younger than 3 years old
4. Duration of protection in children
5. Efficacy, effectiveness and safety of booster vaccination in children

References

[1] US CDC. COVID-19 Information for Pediatric Healthcare Providers [Internet]. [cited 2021 Sep 17]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html.

[2] American Academy of Pediatrics. Children and COVID-19: State-Level Data Report [Internet]. [cited 2021 Sep 17]. Available from: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report

[3] Wallace M, Woodworth K, Gargano J, Scobie H, Blain A, Boulia D. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine in adolescents aged 12–15 Years — United States, May 2021. MMWR Morb Mortal Wkly Rep. 2021;70(20):749–52.

[4] Lv M, Luo X, Shen Q, Lei R, Liu X, Liu E. Safety, immunogenicity, and efficacy of COVID-19 vaccines in children and adolescents: a systematic review. Vaccines [Internet]. 2021 [cited 2021 Sep 17];9(10):1102. Available from: https://doi.org/10.3390/vaccines9101102.

[5] Frenck R, Klein N, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/a5820eb1dc7757b8f2376b5857ab253f3a8c5a62

[6] Ali K, Berman G, Zhou H, Deng W, Faughnan V, Coronado-Voges M, et al. Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. N Engl J Med [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/71d40df3cbe241937f0ed4b8f0bec9ce89c2ecbd

[7] Han B, Song Y, Li C, Yang W, Ma Q, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. Lancet Infect Dis [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/b469151fbe2d8574e3f680501b44ed50c82fafdf

[8] Bickel S, Harris C, Huxol H, R M. COVID-19 Vaccination Outcomes at a Pediatric Long-Term Care Facility. Pediatr Infect Dis J. 2021;40(7):e281-3.

[9] Revon-Riviere G, Ninove L, Min V, Rome A, Coze C, Verschuur A, et al. The BNT162b2 mRNA COVID-19 vaccine in adolescents and young adults with cancer: A monocentric experience. Eur J Cancer [Internet]. 2021;154:30–4. Available from: http://www.epistemonikos.org/documents/8bf6a5f88d3f26a084be7236c5cb9184f670b69a

[10] Delahoy M, Ujamaa D, Whitaker M, A O, Anglin O, Burns E. Hospitalizations associated with COVID-19 among children and adolescents — COVID-NET, 14 States, March 1, 2020–August 14, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(36):1255–60. Available from: https://doi.org/10.15585/mmwr.mm7036e2.

[11] Siegel D, Reses H, Cool A, Shapiro C, Hsu J, Boehmer T. Trends in COVID-19 cases, emergency department visits, and hospital admissions among children and adolescents aged 0–17 years — United States, August 2020–August 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1–6.

[12] Hause AM, Gee J, Baggs J, Abara WE, Marquez P, Thompson D, et al. COVID-19 Vaccine Safety in Adolescents Aged 12-17 Years - United States, December 14, 2020-July 16, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(31):1053–8. Available from: https://dx.doi.org/10.15585/mmwr.mm7031e1

[13] Diaz G, Parsons G, Gering S, Meier A, Hutchinson I, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19 [Internet]. JAMA. 2021 [cited 2021 Sep 5]. Available from: https://jamanetwork.com/journals/jama/fullarticle/2782900

[14] Gargano J, Wallace M, Hadler S, Langley G, Su J. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on

Immunization Practices — United States, June 2021. Morbidity Mortality Weekly Report. 2021.

[15] Pepe S, Gregory A, Denniss A. Myocarditis, pericarditis and cardiomyopathy after COVID-19 vaccination. Hear Lung Circ. 2021;30:1425–9.

[16] Das B, Kohli U, Ramachandran P, HH N, Greil G, Hussain T, et al. Myopericarditis following mRNA COVID-19 Vaccination in Adolescents 12 through 18 Years of Age. J Pediatr [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/80890fa62b48b86edd4a3b974c446c48dbf4e7cb

[17] Schauer J, Buddhe S, Colyer J, Sagiv E, Law Y. Myopericarditis after the Pfizer mRNA COVID-19 Vaccine in Adolescents. The Journal of pediatrics.

[18] Snapiri O, C RD, Shirman N, Weissbach A, Lowenthal A, Ayalon I, et al. Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine. Pediatr Infect Dis J [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/e1edf775714d7c01efaf2c6400720cf7d0a350fa

[19] Tano E, S SM, Girgis S, Martinez-Fernandez Y, C SV. Perimyocarditis in Adolescents After Pfizer-BioNTech COVID-19 Vaccine. J Pediatric Infect Dis Soc [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1225cbdcd1bb81b538ce18a4d78965ab7e6a2161

[20] US FDA. Emergency use authorization (EUA) of the Pfizer-Biontech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID019). [Internet]. [cited 2021 May 11]. Available from: https://www.fda.gov/media/144413/download

[21] European Medicines Agency. CHMP extention of indication variation assessment [Internet]. [cited 2021 Aug 10]. Available from: https://www.ema.europa.eu/en/documents/variation-report/spikevax-previously-covid-19-vaccine-moderna-epar-chmp-extension-indication-variation-assessment_en.pdf

[22] WHO. COVID-19 advice for the public: Getting vaccinated. July 14, 2021 [Internet]. [cited 2021 Aug 9]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice.

[23] Campos-Outcalt D. ACIP recommendations for COVID-19 vaccines—and more. J Fam Pract. 2021;70(2):86–92.

[24] National Advisory Committee on Immunization. Recommendation on the use of mRNA COVID-19 vaccines in adolescents 12 to 17 years of age.

[25] JCVI statement on COVID-19 vaccination of children and young people aged 12 to 17 years: 4 August 2021.

[26] Singapore Ministry of Health. Child vaccination. [Internet]. [cited 2021 Sep 17]. Available from: https://www.moh.gov.sg/covid-19/vaccination/faqs---children-related-vaccination-matters

[27] PPS-PIDSP Statement on COVID-19 Vaccines for Children. 6 September 2021 [Internet]. [cited 2021 Oct 20]. Available from: http://www.pidsphil.org/home/wp-content/uploads/2021/09/Updated-PPS-PIDSP-Statement-on-COVID-19-Vaccination-in-Children-Sept-2021.pdf

[28] Marshall M, Ferguson I, Lewis P, Jaggi P, Gagliardo C, JS C. Symptomatic acute myocarditis in 7 adolescents after Pfizer-BioNTech COVID-19 vaccination. Vol. 148, Pediatrics. 2021. p. e2021052478.

[29] Lane S. Reports of myocarditis and pericarditis following mRNA COVID-19 vaccines: A review of spontaneously reported data from the UK, Europe, and the US. medRxiv2. 2021.

[30] WHO. The Pfizer BioNTech (BNT162b2) COVID-19 vaccine: What you need to know.

September 2, 2021 [Internet]. [cited 2021 Sep 17]. Available from: https://www.who.int/news-room/feature-stories/detail/who-can-take-the-pfizer-biontech-covid-19--vaccine

Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)					
Benefits	Large (3)	Moderate (6)	Small	Uncertain (1)			• BNT162b2 (Pfizer) vaccine efficacy of 100% (95% CI 78.0-100.0) at least 7 days after the second dose.
Harm	Large (2)	Small (4)	Uncertain (4)				• Local and systemic adverse events were reported. • Myocarditis: adverse event of special interest for mRNA vaccines, particularly in children.
Certainty of evidence	High	Moderate (6)	Low (4)	Very Low			• Very low to moderate
Balance of effects	Favors vaccine (9)	Does not favor vaccine	Uncertain (1)				• Benefit of vaccination still outweigh risks, including the risk of myocarditis after vaccination, for all age groups.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (8)	Possibly no important uncertainty or variability	No important uncertainty or variability			• Vaccination coverage in the Philippines (as of October 11, 2021): 26,486,522 have had 1 dose; 23,186,969 have completed 2nd dose & single-dose vaccines.
Resources required	Uncertain	Large cost (5)	Moderate cost (5)	Negligible cost or savings	Moderate savings	Large savings	• Average composite cost of around PHP 1,300.00 per person for the vaccination program. • The mRNA vaccines require ultra-low freezer (between -90°C and -60°C for BNT162b2; -50°C and -15°C for mRNA-1273). • For the CoronaVac vaccine, it can be stored at 2° to 8°C for 6 months.
Certainty of evidence of resources required	No included studies (7)	Very low (1)	Low (1)	Moderate (1)	High		

Cost effectiveness	No included studies (9)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (2)	Reduced (3)	Probably no impact	Increased (5)			• Available through the designated hospitals / local government units (LGUs).
Acceptability	Uncertain (2)	No	Yes (8)				• DOH confirmed that pediatric vaccination using Pfizer and Moderna will start among 12 to 17 year olds with comorbidities as part of Priority Group A3 (9/30/21) • Issues surrounding vaccine hesitancy are due to exposure to negative media information (related to the dengue vaccine) and concerns about vaccine safety.
Feasibility	Uncertain (2)	No	Yes (8)				

Appendix 2. Characteristics of Randomized Clinical Trials on COVID-19 in Children

Study ID	Population	Intervention	Comparator	Outcomes
Frenck et al.[5] Ph. 3	12 to 15 years old, healthy or had stable preexisting disease (N = 2,264)	BNT162b2 30 ug in 0.3 mL x 2 doses, 3 weeks apart (N = 1,134)	0.9 NSS 0.5 mL x 2 doses (N = 1,130)	Efficacy - VE against confirmed COVID-19, 7 days or more after dose 2 Immunogenicity (1 month after dose 2) - SARS-CoV-2 serum neutralization assay - Receptor-binding domain [RBD]–binding or S1-binding IgG - GMT rise from baseline to 1 month after dose 2 Safety - Local and systemic reactogenicity events 7 days after each dose - Serious adverse events 1 month and 6 months after dose 2
Ali et al.[6] Ph. 3	12 to <18 years old, in good health (N = 3,732)	mRNA-1273 100 ug in 0.5 mL x 2 doses, 28 days apart (N = 2,139)	0.9 NSS 0.5 mL (N = 1,243)	Efficacy - VE against confirmed COVID-19 14 days after dose 2 - VE against asymptomatic SARS-CoV-2 infection Immunogenicity - Neutralizing antibody titer - SARS-CoV-2 spike protein antibody - GMT, seroresponse rate 28 days after dose 2 Safety - Local and systemic adverse reactions 7 days after each dose - Unsolicited adverse events (AEs) from days 1 to 28 - Medically attended adverse events, adverse events leading to withdrawal, serious adverse events, data on MIS-C collected until end of the trial

Study ID	Population	Intervention	Comparator	Outcomes
Han et al.[7] Ph. 1, 2	3-17 years old, healthy (Ph 1: 72, Ph 2: 480)	CoronaVac 1.5 ug / 3.0 ug in 0.5 mL x 2 doses, 28 days apart (Ph1: 36; Ph 2: 1.5 ug = 192; 3.0 ug = 192)	Aluminum hydroxide only (Ph 1: 36; Ph 2: 96)	Immunogenicity - Seroconversion rate (for neutralizing antibodies at day 28 after D2) - GMT of neutralizing antibodies to live SARS-CoV-2 - Seropositive rates - Geometric mean increase Safety - Solicited adverse events within 7 days - Unsolicited adverse events within 28 days, follow up until 12 months - Serious AE - Abnormal changes in labs at day 3 after each dose

Appendix 3. Detailed Study Appraisals of RCTs

Risk of Bias Assessment for Frenck et al.

Parameter	Basis	Assessment
Random sequence generation	Interactive web-based response system	Low
Allocation concealment	Interactive web-based response system	Low
Blinding of participants and personnel	Yes (triple-blinded)	Low
Blinding of outcome assessment	Yes (triple-blinded)	Low
Incomplete outcome data (efficacy)	Interim report, 2 month median follow up data reported (planned 1 year assessment	High / unclear*
Incomplete outcome data (safety)	Interim report, 2 month median follow up data reported (planned 1 year assessment	High / unclear*
Selective reporting	All planned outcomes reported	Low

Risk of Bias Assessment for Ali et al.

Parameter	Basis	Assessment
Random sequence generation	Centralized interactive response technology	Low
Allocation concealment	Access to code controlled at pharmacy level	Low
Blinding of participants and personnel	Yes	Low
Blinding of outcome assessment	Yes	Low
Incomplete outcome data (efficacy)	Interim report, 2 month median follow up data reported	High / unclear*
Incomplete outcome data (safety)	Interim report, 2 month median follow up data reported	High / unclear*
Selective reporting	All planned outcomes reported	Low

Risk of Bias Assessment for Han et al.

Parameter	Basis	Assessment
Random sequence generation	Randomization codes generated by the randomization statistician using SAS software	Low
Allocation concealment	Randomization code assigned to each participant in sequence in the order of enrollment	Unclear
Blinding of participants and personnel	Participants and investigators masked	Low
Blinding of outcome assessment	Investigators and laboratory staff masked	Low
Incomplete outcome data (efficacy)	Interim analysis, planned follow up to 12 months after dose 2	High / unclear*
Incomplete outcome data (safety)	Interim analysis, planned follow up to 12 months after dose 2	High / unclear*
Selective reporting	All planned outcomes reported	Low

Appendix 4. Summary of Findings and GRADE Tables

1. BNT162b2 (Pfizer)

COMPARISON : BNT162b2 (Pfizer) vs placebo in Children (12-15 years)									
Efficacy Outcome (at >7 days after dose2)	**Quality Assessment**					**Summary of Findings**			**Certainty**
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	
1.1. Symptomatic COVID-19 infection *without evidence of previous infection*	With concerns (interim report)	Not assessed	Not serious	Not serious	With concerns	0/1005	16/978	100% (75.3,100.0)	+++ Moderate
1.2. Symptomatic COVID-19 infection *with or without evidence of previous infection*	With concerns (interim report)	Not assessed	Not serious	Not serious	With concerns	0/1119	18/1110	100% (78.1, 100)	+++ Moderate
2. Severe COVID-19 infection	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
3. COVID-19 infection, postD1, preD2	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
4. Asymptomatic COVID-19 infection	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
5. Hospitalization	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
6. ICU Admission	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na
7. Death due to COVID-19	With concerns (interim report)	Not assessed	Not assessed	Not assessed	Not assessed	Na	Na	Na	Na

COMPARISON : BNT162b2 (Pfizer) vs placebo in Children (12-15 years)									
Safety Outcome	Quality Assessment					Summary of Findings			Certainty
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	
1. Adverse reaction	Not serious	Not assessed	Not assessed	Not assessed	Not serious	na	na	na	na
2. Local adverse reaction	Not serious	Not assessed	Not assessed	Not assessed					++++ High
3. Systemic adverse reaction	Not serious	Not assessed	Not assessed	Not assessed					++++ High
4. Adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	68/1131	67/1129	1.01 (0.73 1.41)	++ Low
5. Severe adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	7/1131	2/1129	3.49 (0.73, 16.78)	++ Low
6. Serious adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	4/1131	1/1129	3.99 (0.45, 35.67)	++ Low
7. Related serious adverse event	With concerns (interim report)	Not assessed	Not assessed	No cases	Not assessed	0	0	0	na
8. Withdrawals due to adverse event	With concerns (interim report)	Not assessed	Not assessed	Serious	Serious	2/1131	0/1129	4.99 (0.24, 103.85)	++ Low
9. Death	With concerns (interim report)	Not assessed	Not assessed	No cases	Not assessed	0	0	0	na

2. mRNA-1273 (Moderna)

COMPARISON : mRNA-1273 vs placebo in Children (12 to <18years old)									
Efficacy Outcome (at >14days after dose2)	**Quality Assessment**					**Summary of Findings**			**Certainty**
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Vaccine Efficacy**	
1: Symptomatic COVID-19 infection	With concerns (interim report)	Not assessed	Not serious	Serious (wide CI)	Serious	0/2163	4/1073	100 (28.9, NE)	++ Low
2 : Severe COVID-19 infection	With concerns (interim report)	Not assessed	Not serious	No cases	Not assessed	Na	Na	Na	Na
3 : COVID-19 infection, postD1, preD2	With concerns (interim report)	Not assessed	Not serious	No cases	Not assessed	Na	Na	Na	Na
4. Asymptomatic COVID-19 infection (mITT)	With concerns (interim report)	Not assessed	Not serious	Serious (wide CI)	Serious	25/2163	29/1073	59.5% (28.4, 77.3)	++ Low
5 : Hospitalization	With concerns (interim report)	Not assessed	Not assessed	No event	Not assessed	Na	Na	Na	Na
6 : ICU Admission	With concerns (interim report)	Not assessed	Not assessed	No event	Not assessed	Na	Na	Na	Na
7 : Death due to COVID-19	With concerns (interim report)	Not assessed	Not assessed	No event	Not assessed	Na	Na	Na	Na

COMPARISON : mRNA-1273 vs placebo in Children (12 to <18years old)									
Safety Outcome	Quality Assessment					Summary of Findings			Certainty
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Assessment	Vaccine	Control	Relative Risk	
1. Adverse reaction	Not reported	Not assessed	Not serious	Not reported	Not assessed	na	na	na	na
2.1. Local adverse reaction after dose 1	Not serious	Not assessed	Not serious	Not serious	Not serious	2339/2482	455/1238	2.56 (2.38, 2.76)	++++ High
2.2. Local adverse reaction after dose 2	Not serious	Not assessed	Not serious	Not serious	Not serious	2314/2478	398/1220	2.86 (2.64, 3.11)	++++ High
3.1. Systemic adverse reaction after dose 1	Not serious	Not assessed	Not serious	Not serious	Not serious	1701/2482	687/1238	1.24 (1.17, 1.31)	++++ High
3.2. Systemic adverse reaction after dose 2	Not serious	Not assessed	Not serious	Not serious	Not serious	2134/2478	561/1220	1.90 (1.78, 2.02)	++++ High
4. Adverse event	With concerns (interim report)	Not assessed	Not serious	Not serious	Serious	510/2485	197/1240	1.17 (1.12, 1.22)	+++ Moderate
5. Severe adverse event	With concerns (interim report)	Not assessed	Not serious	Serious	Serious	4/2486	1/1240	2.0 (0.22, 17.83)	++ Low
6. Serious adverse event	With concerns (interim report)	Not assessed	Not serious	Serious	Serious	2/2485	1/1240	0.54 (0.03, 8.67	++ Low
7. Related serious adverse event	With concerns (interim report)	Not assessed	Not serious	No cases	With concerns	0	0	na	na
8. Withdrawals due to adverse event	Not reported	Not assessed	Not serious	Not assessed	Not assessed	na	na	na	na
9. Death	With concerns (interim report)	Not assessed	Not serious	No cases	With concerns	0	0	na	na

3. Coronavac (Sinovac)

COMPARISON : Coronavac (Sinovac) vs placebo in Children (3 to 17 years old) using 0.3ug									
Safety Outcome	**Quality Assessment**					**Summary of Findings**			**Certainty**
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Overall Assessment**	**Vaccine**	**Control**	**Relative Risk**	
1. Adverse reaction	Serious (unclear concealment)	Not assessed	Not serious	Serious	Serious	59/217	22/114	1.41 (0.91, 2.17)	++ Low
2. Local adverse reaction	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
3. Systemic adverse reaction	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
4. Adverse event	Very Serious (unclear concealment) (interim report)	Not assessed	Not serious	Serious	Very Serious	15/217	9/114	0.88 (0.40, 1.94)	+ Very Low
5. Severe adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
6. Serious adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
7. Related serious adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
8. Withdrawals due to adverse event	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na
9. Death	Not reported	Not assessed	Not assessed	Not assessed	Not assessed	na	na	na	na